REMARKS

In the outstanding Office action, claims 1-7 and 9-30 were presented for examination. Claims 1-7 and 9-30 were rejected.

In this amendment, applicant has amended claims 1, 9, 10, 12, 15, 19, 21, 24, 25, 26 and 28, and has cancelled claims 2 and 29, without prejudice. New claims 31 and 32 have been added. Accordingly, claims 1, 3-7, 9-28 and 30-32 are now pending for examination and, as will be discussed in detail below, it is believed that the application is in condition for allowance. Favorable reconsideration of the claims now pending is respectfully requested.

Claim Amendments

Claims 2 and 29 have been cancelled.

Claims 1 and 9 have been amended to recite the limitation appearing in now-cancelled claim 2 that the recombinant or synthetic gelatin-like polypeptide has a molecular weight between 3,000 Dalton and 80,000 Dalton.

Claims 10, 12, 15, 19, 21 and 24 have been amended to change their dependencies from now-cancelled claim 2 to claim 1.

Claim 24 has been amended to add the phrase "identical to or". Support for this amendment can be found at page 10, line 6 of applicant's specification.

In addition Claim 24 has been amended to recite that the region of the amino acid sequence of a native collagen is a "selected" region and to recite that the selected region has a calculated average glass transition temperature higher than the calculated average glass transition temperature of the complete native collagen by at least about 10 degrees Celsius. Support for this amendment can be found at page 8, lines 21-26 of applicant's specification.

Minor amendments of a clerical nature have been made to claim 25.

Claim 26 has been amended for better consistency with the specification at page 5, lines 21-26, thereby making explicit subject matter that was inherent in claim 26 before amendment. In addition, the temperature limitation of "about 10 degrees Celsius" has been deleted as this limitation now appears in parent claim 24.

Claim 28 has been amended, without narrowing, to remove unnecessary language.

New claim 31 has been added. New claim 31 depends from claim 9 and recites selecting the recombinant or synthetic gelatin-like polypeptide to have an amino acid sequence identical to or essentially similar to a selected region of a native collagen sequence. Support for new claim 31 can be found at page 5, lines 19-28, of applicant's specification.

New claim 32 has been added. New claim 32 depends from claim 31 and recites a manner of identifying the amino acid region by calculation of a moving average glass transition temperature. Support for new claim 32 can be found at page 8, lines 15 to 23 of applicant's specification.

Claim Rejections - 35 U.S.C. § 112 Second Paragraph

The Office action rejects claims 24-30 35 U.S.C. § 112 second paragraph as allegedly being rendered indefinite by the use of the terms "essentially similar" and "region" in claims 24 and 30.

In reply, applicant respectfully submits that claims 24-30, as now amended, are clear.

Applicant's intended meaning of the term "essentially similar" is explained in detail at page 10, lines 5-16 of applicant's specification. In light of this definition, applicant respectfully submits that the specification contains sufficient guidelines and examples to enable a person of ordinary skill in the art to draw a line between amino acid sequences which are essentially similar to a selected region of a native collagen sequence and those which are not. Accordingly, the term "essentially similar", as used in claims 24 and 30 is clear, applicant believes.

The term "region" is now qualified as being a "selected" region and the selected region is further defined as having a calculated average glass transition temperature higher than the calculated average glass transition temperature of the complete native collagen by at least about 10 degrees Celsius. Accordingly, the term "region", as used in amended claims 24 and 30 is clear, applicant believes.

Furthermore, applicant believes that a person of ordinary skill in the art will understand the term "region" to refer to a part of the whole, which is something less than the whole, much as the constant region and the variable region are mere parts of an antibody molecule, not the whole molecule.

Therefore, applicant respectfully submits that the construction of the term "region" of the native collagen sequence employed in paragraph (3a) on page 8 of the Office, as embracing the full-length native collagen sequence, or the full length native sequence minus 1-2 amino acid residues, is inappropriate. The Office is respectfully requested to construe the term "region" in the manner utilized in applicant's specification, as further elucidated here.

Claim Rejections - 35 U.S.C. § 103 Alleged Unpatentability

In the outstanding Office action, claims 1-7 and 9-30 were rejected under 35 U.S.C. § 103 as allegedly being unpatentable over International Publication No. WO 01/34801, referenced as "Chang et al.", in view of Wang 2000 International Journal of Pharmaceutics 203 (2000) 1-60, referenced as "Wang". Matveev et al. (previously cited) was relied upon in the Office action "as evidence that gelatin has a glass transition temperature of 200° C".

In reply, applicant respectfully submits that claims 1 and 9, as now amended, are patentably distinguished from any combination of Wang with Chang et al., notwithstanding the teachings of Matveev et al., for reasons which will now be explained.

Referring to the Office action, the helpful reply comments appearing at pages 7-8 are appreciated by applicant and have been carefully considered.

From the comments in paragraph 3a on page 8 of the Office action, applicant understands that the Office has construed claims 1 and 9 to embrace a full-length native collagen sequence or a full-length native collagen sequence "minus one or two amino acids". A full-length recombinant gelatin such as Col1A1 would have a molecular weight of at least about 140,000 Dalton, applicant believes, and would be excluded from the scope of claims 1 and 9, as these claims are now amended. This is because claims 1 and 9 are now limited to using a recombinant or synthetic gelatin-like polypeptide stabilizer that has a molecular weight between 3,000 Dalton and 80,000 Dalton.

Therefore, having regard to the new molecular weight limitation appearing in claims 1 and 9, grounds of rejection based upon disclosures of such full-length native collagen sequences are now moot, applicant submits. Accordingly, applicant also respectfully submits that amended claims 1 and 9 are unobvious and therefore patentable over Chang et al. in view of Wang, for this reason alone. Additional reasons for the patentability of amended claims 1 and 9 are explained below.

The Office action states (on page 5) that it would have been obvious to modify the teachings of Chang et al. by producing a lyophilized composition employing a recombinant gelatine having a polypeptide sequence that is a native mammalian collagen sequence having a high glass transition temperature (as suggested by Wang).

Applicant respectfully disagrees. Chang et al. has been discussed previously on the record herein. Chang et al. discloses the use of recombinant gelatins (having a large range of molecular weights) as stabilizers in pharmaceutical compositions, in particular in vaccines. Chang et al.'s disclosure is exemplified by gelatins having molecular weights in the range of 5-65 kDa (page 69, Table 2 of Chang et al.).

As is apparent from applicant's specification at page 9, lines 9-11 and from Chang et al.'s specification at page 61, lines 27-33, and page 65, lines 21-25, native gelatin compounds used as stabilizers for pharmaceutical compositions, prior to the availability of recombinant gelatins, were

generally hydrolyzed gelatins having a molecular weight substantially less than that of native gelatin.

As acknowledged on page 4 of the Office action, Chang et al. does not teach a glass transition temperature for gelatin. However, as stated in the Office action, Matveev does provide a glass transition temperature for a gelatin. Nevertheless, the glass transition temperature (sometimes "Tg" herein) for a food gelatin described by Matveev does not appear to be that of a hydrolyzed gelatin compound that might have been used as a protein stabilizer. Rather, the Tg provided by Matveev appears to be that of a native non-hydrolyzed food gelatin. However, such a full-length recombinant gelatin is now excluded from the scope of claims 1 and 9 by the limitation of the molecular weight to be between 3,000 and 80,000 Dalton, and the Tg of hydrolyzed gelatin, which was known as a stabilizer in pharmaceutical compositions, was unknown to skilled person, prior to applicant's claimed invention, applicant believes.

Accordingly, Matveev does not appear to help the worker considering Chang et al to improve the stability of a lyophilized physiological composition.

Furthermore, Chang et al. also does not provide knowledge of the relationship between the glass transition temperature and the improved stability of a lyophilized physiological composition that can be obtained by employing in the lyophilized composition a recombinant or synthetic polypeptide which might suggest to a skilled worker the invention claimed in applicant's claims 1 and 9.

Still further, as applicant showed in the Amendment-after-final filed on September 24, 2008, Chang et al. does not disclose a synthetic or recombinant gelatin-like polypeptide having a glass transition temperature higher than 180 degrees Celsius, as is required by applicant's amended claims 1 and 9. And Chang et al. does not disclose or suggest a method of preparing a synthetic or recombinant gelatin-like polypeptide having a glass transition temperature higher than 180 degrees Celsius.

Wang does not appear to correct these deficiencies of Chang et al. as will now be explained. Wang does not appear to provide a clear teaching, or suggestion, to a person of ordinary skill in the art that the stability of a lyophilized composition comprising a physiologically active agent can be improved by employing in the composition a synthetic or recombinant gelatin-like polypeptide having a relatively high glass transition temperature.

Wang describes the lyophilization and development of solid protein pharmaceuticals. With regard to the stability of these compositions, Wang et al. states the following:

> Several factors can affect the stability of solid protein pharmaceuticals. These include storage temperature, glass transition temperature, formulation pH, residual moisture content, type and concentration of formulation excipients, and crystallization of amorphous constituents. *(Page 28, lefthand column of Wang et al.)*

Here, Wang et al. identifies glass transition temperature as one of a number of factors, six are noted, that can affect the stability of solid protein pharmaceuticals. Each of the six factors, together with a seventh (reconstitution medium) is discussed in substantial detail by Wang at pages 28-35 and reasons are given as to why each factor can affect the stability of a solid protein pharmaceutical. Any and all of the factors discussed apparently need to be taken into account by a worker considering how to improve the stability of a solid protein pharmaceutical.

Accordingly, Wang does not provide clear guidance or suggestion to a person of ordinary skill in the art that the stability of a lyophilized pharmaceutical composition can be improved by employing a synthetic or recombinant gelatin-like polypeptide having a calculated glass transition temperature higher that 180° C, as defined in applicant's amended claims 1 and 9. Rather the number of stability-related factors identified by Wang and the nature of the discussion of each, would suggest to a person of ordinary skill in the art that controlling the stability of a solid protein pharmaceutical is a complex problem, in applicant's view.

Wang mentions gelatin in Table 1 on page 19 as one among a number of possible excipients for such solid protein pharmaceuticals (pages 18-20 of Wang et al.). However, no Tg is given for gelatin by Wang.

Moreover, Wang's guidance regarding the role of glass transition temperature in the stability of solid protein pharmaceutical is equivocal, applicant believes. Thus, Wang states with respect to Tg:

> Generally, the higher the glass transition temperature, the more stable the protein formulation. (*Page 29, lefthand column, first paragraph*).

and:

> How well can Tg be used to predict stability of solid protein pharmaceuticals? Mixed results have been obtained. *(Page 29, lefthand column, final paragraph.)*

and:

> However, there are many examples where formulations of a lower Tg are more stable than those of a higher Tg. *(Page 29, righthand column, middle section.)*

Indeed, Wang appears to be uncertain as to the role of Tg in the stability of a solid protein formulation because mixed results have been obtained and some formulations with a lower Tg are more stable, according to Wang.

Therefore, applicant believes that a person of ordinary skill in the art, knowing from Chang et al. that a recombinant gelatin can be used as a stabilizer in pharmaceutical compositions, would not consider the teachings of Wang et al. This is because Wang does not provide a person of ordinary skill in the art with a reasonable expectation of success that increasing the Tg will result in an improved stability of solid protein pharmaceuticals. Instead, Wang appears to suggest that many factors are implicated in the stability of solid protein pharmaceuticals and that the role of the Tg is uncertain.

In summary, Wang does not appear to suggest employing a recombinant gelatine having a polypeptide sequence that is a native mammalian collagen sequence having a high glass transition temperature to improve the stability of a lyophilized physiological composition, as is stated on page 5 of the Office action. Accordingly, applicant respectfully requests that rejections based upon this statement in the Office action, or upon similar statements, be withdrawn. Applicant has noted similar statements in the middle and toward the end of the long paragraph on page 5, at page 8, lines 3-4 and in paragraph (4a) on page 8 of the Office action. Others may exist.

The Office action also states on page 5 that the recombinant gelatin is to have the same functional and/or structural characteristics as the native collagen, pursuant to Chang et al., i.e. a glass transition temperature of 200° C (as evidenced by Matveev et al.). However, applicant is unaware of any disclosure on the record of a synthetic or recombinant gelatin-like polypeptide having a glass transition temperature of higher than 180° C, yet alone 200° C.

Applicant's specification discloses, at page 3, lines 29-31 that, in general, native collagen peptides have a calculated Tg of about 170 degrees Celsius or less. Col1A1 has a glass transition temperature of about 163° C, as stated at page 7, line 8 of applicant's specification and applicant showed previously that the polypeptide sequences disclosed in Chang et al.'s examples all have calculated glass transition temperatures below 180° C. Therefore, it appears that the 200° C Tg described by Matveev et al. for a food gelatin was not known for a synthetic or recombinant gelatin-like polypeptide, prior to applicant's claimed invention.

Nor does the art prior to applicant's claimed invention describe a method of providing a synthetic or recombinant gelatin-like polypeptide with a calculated glass transition temperature higher than 180° C, applicant believes. Accordingly, this statement in the Office action appears to be unsupported and applicant respectfully requests that rejections based upon it also be withdrawn.

Applicant's invention as now claimed in amended claims 1 and 9 comprises substantially more than is disclosed by any combination of Chang et al. with Wang, and is therefore unobvious and patentable, applicant believes. Neither Chang et al. nor Wang plainly correlates an improved stability of a lyophilized physiological composition with a synthetic or recombinant gelatin-like polypeptide having a relatively high glass transition temperature. Neither Chang et al. nor Wang discloses a synthetic or recombinant gelatin-like polypeptide having a calculated glass transition temperature of higher than 180 degrees Celsius as is recited in applicant's. Neither Chang et al. nor Wang provides a method of preparing a synthetic or recombinant gelatin-like polypeptide having a glass transition temperature of higher than 180 degrees Celsius. And neither Chang et al. nor Wang discloses that the sequence of a native collagen can have a region which has a higher calculated Tg than the calculated Tg of the complete sequence of the native collagen.

For the above reasons, applicant respectfully submits that claims 1 and 9, as now amended, are patentable over Chang et al. in view of Wang, notwithstanding the disclosure of Matveev et al., and are therefore allowable. Favorable reconsideration and allowance of amended claims 1 and 9 are respectfully requested.

Dependent Claims

Claims 3-7 and claims 10-28 and 30 depend from claim 1, either directly or indirectly, and claims 31 and 32 depend from claim 9, either directly or indirectly. Dependent claims 3-7, 10-28 and 31-32 therefore incorporate all the limitations of their respective parent claims and therefore are believed to be allowable for at least the same reasons that claims 1 and 9 are believed to be allowable. Furthermore, dependent claims 3-7, 10-28 and 31-32 are believed clearly and patentably distinguished from the art of record, and therefore allowable, by the additional limitations they recite.

Some of these limitations were discussed in applicant's Amendment-after-final filed on September 24, 2008, and reference is here made to that discussion to the extent applicable to the currently pending claims.

For example, claims 21-23 specifically recite that the calculated glass transition temperature of the recombinant or synthetic gelatin-like polypeptide recited in claim 1, 2 or 3, respectively, is higher than 200 degrees Celsius which applicant believes is neither disclosed nor suggested by Chang et al. as evidenced by Matveev et al. or by Wang.

Claim 24 recites that the complete amino acid sequence of the recombinant or synthetic gelatin-like polypeptide is identical to or essentially similar to a selected region of the amino acid sequence of a native collagen having a higher calculated average glass transition temperature. Claim 30 recites the selection of such a region. Neither Chang et al. nor Wang appears to suggest that such a region even exists.

Claim 32 recites identifying a region of higher calculated average glass transition temperature by calculating a moving average glass transition temperature over a number of amino acids, as defined in the claim. Neither Chang et al. nor Wang remotely contemplates such a process.

Conclusion

In view of the above amendments and the discussion relating thereto, it is respectfully submitted that the instant application, as amended, is in condition for allowance. Favorable reconsideration and allowance are earnestly solicited. If for any reason the Examiner feels that consultation with applicant's representative would be helpful in the advancement of the prosecution, the Examiner is invited to contact the undersigned practitioner.

Respectfully submitted,

By: /Roger Pitt/
Roger Pitt
Reg. No. 46,996
Ph: (212) 536-4867
Fax: (212) 536-3901

(Customer Number 00545)
K&L GATES LLP
599 Lexington Avenue (33rd Floor)
New York, NY 10022-6030